

REMARKS

This is intended to be a complete response to the official action mailed December 22, 2006, in which claims 14-19, 22-41, 55-60 and 63-91 were rejected in a new rejection under 35 U.S.C. § 103(a).

Rejection Under § 103(a)

Claims 14-19, 22-41, 55-60 and 63-91 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hidalgo et al. (*J. Clin. Invest.*, 2002 Vol. 110, pages 559-569, IDS) in view of Kobzdej et al. (*Blood*, 2002, Vol. 100, pages 4485-4494 IDS).

In the rejection, it is stated:

"Hidalgo, et al., teach that homing of human HSCs comprising cells characterized as CD34⁺Cd38^{low/-} is impaired due to inability to bind with P-selectin or E-selectin (see entire document, Abstract in particular). Hidalgo, et al., further teach that said reduced ability to bind is due to a defect in the posttranslational processing of PSGL-1 protein that is expressed on the surface of said cells. Hidalgo, et al., further teach that said posttranslational modification is fucosylation and that forced fucosylation of said cells can be beneficial to improve homing of said cells. (see overlapping pages 568-569 in particular). Hidalgo et al., further teach that improving homing of said cells would have many implications for therapies using human progenitor/stem cells, for example for transplantation.

Hidalgo et al., do not explicitly teach a composition of fucosylated HSCs wherein fucosylated HSCs are produced by treating said cells in vitro with α 1,3 fucosyltransferase in the presence of a fucose donor (emphasis added).

Kobzdej et al., teach a method of forced fucosylation of intact WEHI-3 cells in vitro comprising treating said cells with α 1,3 fucosyltransferase in the presence of a fucose donor (see entire document, Abstract in particular). Kobzdej et al., teach that said

treatment will result in fucosylation of said cells that would enhance their interaction with P-selectin or E-selectin."

Applicants respectfully traverse the rejection for the reasons provided below.

The Hidalgo et al. Reference

Regarding the teachings of Hidalgo et al., it is respectfully noted that several of the Examiner's assertions are incorrect.

Examiner asserts in the rejection, that:

"Hidalgo et al., further teach that said posttranslational modification is fucosylation and that forced fucosylation of said cells can be beneficial to improve homing of said cells." (see overlapping pages 568-569 in particular).

However, this is incorrect. Hidalgo et al. make absolutely no reference to "forced fucosylation" on pp. 568-569, or anywhere else in the article.

Furthermore, in the rejection, it is incorrectly stated that Hidalgo et al., teach that "reduced ability to bind is due to a defect in the posttranslational processing of PSGL-1 protein that is expressed on the surface of [CB-derived CD34⁺] cells" (emphasis added).

What Hidalgo et al. actually do state is:

"Our results suggest that the reduced interactions of CB-derived CD34⁺ cells are due to surface expression of nonfunctional PSGL-1." (p. 568, Col. 1, lines 26-29; emphasis added).

That is, Hidalgo et al. do not positively assert that the reason the non-binding subset of CD34⁺ cells fail to bind to P-selectin is definitely due to

surface expression of faulty PSGL-1; they only suggest it as the reason, and moreover, Hidalgo et al. further undermine confidence in their suggestion by stating:

“the molecular defect responsible for defective PSGL-1 function in the subset of CD-derived CD34⁺ cells remains to be defined” (p. 568, Col. 1, lines 31-33; emphasis added).

Hidalgo et al., do state that in mature leukocytes (not stem cells) posttranslational modifications in PSGL-1 include sialylation, fucosylation and tyrosine sulfation.

However, sialylation, fucosylation and tyrosine sulfation constitute completely separate and distinct enzymatic reactions. Moreover, sialylation and fucosylation are both dependent upon a number of other distinct glycosylation reactions which must occur before the sialylation, fucosylation and sulfation reactions can even be carried out in the cell (see below). Any of these reactions, if faulty, could affect posttranslational processing of PSGL-1. Hidalgo et al. merely identify a few of the many possible “posttranslational defects” which could occur, if indeed defective PSGL-1 was the cause of the impaired binding of the CD34⁺ cells to P-selectin.

Hidalgo et al. thus do not explicitly point to fucosylation as the defective step in the posttranslational processing of the defective CD34⁺ cells. Hidalgo et al. in fact give “equal” weight to sialylation, fucosylation and tyrosine sulfation as steps involved in posttranslational modification of PSGL-1 and

provide absolutely no evidence that fucosylation in particular is deficient in the defective CD34⁺ cells.

The teachings of Hidalgo et al. provide at best an incomplete listing of several of the many steps involved in the posttranslational processing of the PSGL-1 polypeptide. It is well known in the art that there are numerous other glycosylation reactions which must occur even before sialylation and fucosylation, including for example, (1) linking a GalNAc (N-acetylgalactosamine) to an amino acid of the PSGL-1 polypeptide via N-acetylgalactosaminyltransferase; (2) linking a Gal (galactose) to the GalNAc via core1 β 1, 3 galactosyltransferase; (3) linking a GlcNAc (N-acetylglucosamine) to the GalNAc via an N-acetylglucosaminyltransferase, and (4) linking a Gal to the GlcNAc via β 1, 4 galactosaminyltransferase.

Hidalgo et al. identify none of these four crucial steps as potentially causative of the defective posttranslational processing, even though these steps must occur even before the sialylation and fucosylation steps noted by Hidalgo et al.

Most notably, Hidalgo et al. are silent as to which of the posttranslational processing steps is defective, only suggesting (literally) that the posttranslational defect may involve one of these three steps. Further, no data regarding defective fucosylation are provided. Hidalgo et al. thus provide no specific method of rectifying the unspecified defective posttranslational steps

(since, contrary to Examiner's assertion, forced fucosylation is not suggested as a mitigating method) and, Hidalgo et al. most certainly provide no expectation of success of curing the posttranslational defect in the CD34⁺ cells.

As courts have repeatedly held, an "obvious-to-try" standard cannot be used to establish a prima facie case of obviousness. See, for example, *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), or *In re Roemer*, 59 USPQ2d 1527 (Fed. Cir. 2001).

But, as is evident from the above, the teachings of Hidalgo et al. do not rise even to a level of "obvious-to-try" since there is no suggestion in Hidalgo et al. of how to correct the defective PSGL-1 on the CD34⁺ cells.

The Kobzdej et al. Reference

Now, even if, assuming arguendo, the teachings of Hidalgo et al. did suggest defective fucosylation (which they do not, as proven above), a person of ordinary skill in the art would not look to the secondary reference, Kobzdej et al., to modify the teachings of Hidalgo et al.

It is respectfully noted that the Examiner is completely incorrect in his assertion that Kobzdej et al. teach that "said treatment [by fucosylation] of said [CD34⁺] cells would enhance their interaction with P-selectin or E-selectin." In fact, Kobzdej et al. teach exactly the opposite.

In particular, Kobzdej et al., teach that:

- (1) "forced fucosylation of intact cells did not significantly augment their ability to bind to fluid-phase P- or E-selectin or

to roll over immobilized P- or E-selectin under flow” (Abstract; emphasis added);

- (2) “Despite the large increase in sLe^x and Le^x epitopes, forced fucosylation with FTVI either failed to increase or only modestly increased binding of fluid-phase P-selectin or E-selectin to WEHI-3 cells or murine neutrophils (Figure 8).” (p. 4491, 1st complete paragraph of Col. 1; emphasis added);
- (3) “Control and FTVI-treated murine neutrophils also rolled similarly on P- and E-selectin (Figure 10A), resisted detachment from E-selectin equivalently as wall shear stress was increased (Figure 10B), and rolled with similar velocities on P- and E-selectin (Figure 10C-D). Thus, the FTVI-mediated addition of epitopes for sLe^x and Le^x to the surfaces of WEHI-3 cells or murine neutrophils did not significantly augment interactions with P- or E-selectin.” (p. 4491, 1st and 2nd paragraphs of Col. 1; emphasis added);
- (4) “Forced fucosylation with an exogenous α 1-3-fucosyltransferase creates many sLe^x epitopes but does not substantially increase selectin ligands.” (p. 4491, last complete sentence of Col. 2; emphasis added); and
- (5) “It is striking that addition of FTVI and GDP-fucose created many sLe^x epitopes but did not significantly increase selectin ligands” (p. 4492, last three complete sentences of Col. 3; emphasis added).

In view of the above, it is evident that Kobzdej et al. teach away from the present invention and thus are contrary to the examiner’s assertion that it would be obvious to a person of ordinary skill in the art to modify the teachings of Hidalgo et al. with the teachings of Kobzdej et al. to treat the cells of Hidalgo et al. with α 1,3 fucosyltransferase even if Hidalgo et al. suggested forced fucosylation (which it does not).

The teachings of Kobzdej et al. clearly indicate that forced fucosylation does not enhance binding of murine neutrophils and WEHI-3 cells to P- or E-selectin (much less CD34⁺ cells or other stem cells). Kobzdej et al. thus in fact teach away from the present invention. It is well established that references which teach away from the invention are evidence of non-obviousness. A person of ordinary skill in the art, given an understanding of the Kobzdej et al. reference would not be motivated to use forced fucosylation to treat the CD34⁺ cells of Hidalgo et al., in fact, he would be motivated not to do so because Kobzdej et al. teach that there would be no reasonable expectation of success in doing so.

Clearly, given the teachings of Kobzdej et al., a person of ordinary skill in the art would reasonably expect that such fucosylated cells would not have enhanced binding to P- or E-selectin and thus would not be motivated to treat the cells in this manner and indeed would be motivated not to do so.

MPEP § 2143.02 indicates that "a reasonable expectation of success" is required for a determination of obviousness. Yet, as is clear from Kobzdej et al., there is no reasonable expectation of success in view of the contrary teachings that forced fucosylation does not enhance binding of cells to P-selectin or E-selectin, indeed, there would be an "expectation of failure".

In summary, (1) Hidalgo et al. do not demonstrate or state that the defective binding to P-selectin is due to errors in fucosylation of PSGL-1 protein

on CD34⁺ cells and do not teach that forced fucosylation of CD34⁺ cells can be beneficial in improving homing of such cells, and (2) Kobzdej et al. do not teach that forced fucosylation is effective in enhancing binding of murine cells (much less CD34⁺ stem cells) to P-selectin or E-selectin.

As described and explained above, neither the Hidalgo et al., nor Kobzdej et al. references, alone or together, support a conclusion of obviousness.

In view of the above, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the above, applicants submit the claims are now in condition for allowance and request issuance of a Notice of Allowance therefor.

Respectfully submitted,



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